(c) extracting said antigen from said sample with a liquid extraction solution comprising one or two extraction reagents in said assay chamber, wherein said one extraction reagent is added to the assay chamber, to form a liquid extract, or wherein said two extraction reagents are added to said assay chamber in any order, to form a liquid extract;

(d) inserting said sample receiving region into said assay chamber and contacting said liquid extract whereby said liquid extract flows through said labeling situs and then through said capture situs without further addition of reagents or manipulation of said sample; and

(e) determining the presence or absence of said antigen in said sample by detecting the presence or absence of said detectable label at said capture situs.

DRAWINGS

Applicants will delay filing of formal drawings until after receipt of the "Notice of Allowability" (PTO-37).

REMARKS

This invention relates to one-step immunoassays for extracted analytes which permit efficient extraction of analytes from samples, while minimizing sample manipulation following extraction. This permits these assays to be performed by individuals without extensive training in laboratory techniques.

The sample extractions are carried out in assay chambers which are not in flow contact with the sample receiving of the immunoassay device. This permits greater control over mixing of the sample with the extraction reagents, and the duration of the extraction procedure. This added control over extraction conditions permits greater efficiency of extraction, and increased sensitivity of the assay. Moreover, because the extraction is performed in a separate assay chamber, these assays do not require a complex plastic or cardboard housing or specially designed swabs to fit in the complex housings to help control flow of the sample from the sample chamber portion of the housing to the sample receiving region of the immunoassay test strip.

In addition, the claimed immunoassays for an extracted analyte do not require transfer of the sample containing the extracted antigen to the immunoassay device. Furthermore, when two sample extraction reagents are added to the sample chamber, they may be added to the assay chamber in any order, permitting these assays to be performed by individuals without extensive training.

Claims 1-9 are pending. Claims 1-9 have been rejected as indefinite. Claims 1, 2, 4 and 6-9 have been rejected as anticipated by Imrich et al. (U.S. Patent No. 5,415,994). Claims 3 and 5 have been rejected under 35 U.S.C. § 103(a) as unpatentable over Imrich et al. in view of Bogart et al. (U.S. Patent No. 5,494, 801) and Murray (U.S. patent No. 3,957,436). Claims 1-9 have been cancelled. Claims 10-20 are new.

New claims 10-13, and 15-20 correspond substantially to the Examiner's proposed language to clarify claims 1-9. Support therefor is found in the specification

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at, for example, pages 21-25. Applicants have amended the specification to provide the art recognized name for the zwitterionic detergent 3-12, available from Sigma.

Applicants have also added steps (b) and further clarified step (d) of claims 10 and 20 to more clearly state that an immunodiagnostic device and separate assay chambers are provided, and that the immunodiagnostic device is inserted into the assay chamber to contact the liquid extract sample following the extraction step. The liquid extract contacted by the immunodiagnostic device is the liquid extract formed in step (c) by the addition of either one extraction reagent into the assay chamber, or by the addition of two extraction reagents into the assay chamber, depending on whether one or two reagents are added to the assay chamber to extract the sample. Applicants further note that the reagents may be added to the assay chamber before or after the sample is placed in the assay chamber.

Claims 1-9 have been cancelled and claims 10-20 have been added to address the Examiner's concerns regarding the definiteness of the claim language. Applicants respectfully assert that the replacement of claims 1-9 with claims 10-20 does not raise any new issues.

35 U.S.C. § 112:

Applicants believe that claims 10-20 incorporate substantially the Examiner's suggestions for language which recites clear, distinct and positive method steps; eliminates antecedent basis problems, and makes use of consistent terminology. Applicants therefore respectfully assert that the rejections for indefiniteness no longer apply.

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ART BASED REJECTIONS

35 U.S.C. § 102

The Examiner has rejected claims 1, 2, 4 and 6-9 under 35 U.S.C. § 102(b) as anticipated by Imrich et al. (US 5,415,994). Office action mailed 9/2/98 at 7. In the language quoted from Imrich at page 7 of the office action, the devices in Imrich are described as containing an extraction chamber, and as having a test strip matrix in fluid communication with the immunoassay test strip:

> The devices generally comprise an extraction chamber, a labelling zone having a means for specifically labelling the analyte; and a matrix defining an axial flow path in fluid communication with the extraction chamber, which matrix comprises a sample receiving zone and capture zone located downstream from the sample receiving zone. (col. 2, lines 26-32).

Claims 10-20 of the instant application are directed to methods in which an assay chamber separate from the immunoassay device is provided in which to perform the sample extraction. Moreover, in the methods of claims 10-20, the immunoassay device is inserted into the assay chamber to contact the extracted sample after sample extraction, and is not in fluid communication with the assay chamber prior to insertion into the assay chamber.

Furthermore, although Imrich et al. contains language stating that "generally" the devices of Imrich et al. may contain an extraction chamber (col. 2, line 26), or that the immunoassay test matrix is "conveniently" located in a solid casing, Imrich et al. does not describe the use of immunoassay devices other than those containing an extraction chamber in a plastic housing. In addition, although the housing of the exemplary Imrich et al. device is manufactured in a two step procedure, the first step of the process

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results in a device having a plastic bottom portion containing the extraction chamber and the test strip, while in the second step the two halves of the device are assembled:

> The test strip was then placed in a device of the present invention. A 0.29' disc of filter paper (Whatman #114) was inserted into the exit orifice of the extraction chamber.
>
> * * *
>
> The test strip was centered in the bottom portion of the device. The top plate was aligned and snapped into place." Col. 11, lines 22-24.

Imrich thus describes the two step assembly of a device having a single plastic housing which contains the extraction chamber and the test strip in a plastic housing. Even if the second part of this process were omitted, the Imrich "device" would still comprise an open plastic housing containing an extraction chamber and the test strip.

Applicants therefore respectfully assert that none of the instant claims are anticipated by Imrich et al.

35 U.S.C. § 103

Applicants also respectfully assert that none of the claims are made obvious by Imrich et al.

Although the Federal Circuit noted in Interconnect Planning Corp. v. Feil, 227 U.S.P.Q. (BNA) 543 (Fed. Cir. 1985) that the claimed invention and references must each be evaluated as a whole, the Federal Circuit concluded that the district court had improperly reconstructed the claimed invention from separate components in the prior art:

> "From its discussion of the prior art it appears to us that the court, guided by the defendants, treated each reference as teaching one or more of the specific components for use in the Feil system, although the Feil system did not

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then exist. Thus the court reconstructed the Feil system, using the blueprint of the Feil claims. As is well established, this is legal error. Id. at 548.

Moreover, the Federal Circuit further noted that "[t]here must be 'something in the prior art as a whole to suggest the desirability, and thus the obviousness, of making the combination'." Id. at 551 (quoting Lindemann Maschinenfabrik GmbH v. American Hoist and Derrick Co., 730 F2d 1452, 1462, 221 USPQ 481, 488 (Fed. Cir. 1984)).

The test that the prior art must be viewed as a whole avoids improper focus on the obviousness of substitutions and differences between the claimed invention and the prior art. Gillette Co. v. S.C. Johnson & Son, 919 F.2d 720, 16 U.S.P.Q.2d (BNA) (Fed. Cir. 1990). Thus, there must be some reason for combining elements other than hindsight reconstruction. Interconnect Planning Corp. at 551.

Moreover, an invention is not unpatentable because it was "obvious to try." In re O'Farrell, 853 F.2d 894, 902, 7 U.S.P.Q. (BNA) 337 (Fed. Cir. 1988).

Here, as discussed above, Imrich describes only the use of devices containing both the immunoassay test strip and an extraction chamber in fluid communication with the test strip. Imrich does not explicitly describe or suggest a method for detecting a Strep A antigen where the assay chamber is separated from the immunoassay device.

In the instant device, however, spatial separation of the assay chamber from lateral flow contact with the sample receiving region of the lateral flow immunochromatographic assay test strip permits greater control over the length and efficiency of extraction, and the sensitivity of the assay. For example, as noted at page 63 of the specification, a device within the scope of the claimed invention is able to detect Streptococcus cells when present at a concentration as low as 4×10^5 per swab, while the one-step Quidel device can detect Streptococcus cells only when present at a

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concentration of 8 X 10^5 cells/swab. In addition, in a study comparing the sensitivity of the OSOM™ Strep A test with the sensitivity of the Quidel QuickVue™ Strep A test, Dr. Richard H. Schwartz determined that the OSOM™ Strep A test had an overall sensitivity of 95%, while the QuickVue™ Strep A test had an overall sensitivity of 87%. Declaration of Richard H. Schwartz at ¶ 3; Schwartz, Richard H., Pediatric Infectious Disease J., 16(11):1099-1100 (November 1997), Exhibit 2 to the Declaration of Richard H. Schwartz.

The OSOM™ Strep A immunodiagnostic test strips are not contained in a bulky plastic or cardboard housing, and are therefore compact enough to be directly inserted into a sample chamber small enough to permit efficient sample extraction. (Declaration of Richard H. Schwartz at ¶ 4). Also, because the time from the start of the sample extraction to initiation of the lateral flow immunoassay can be controlled by controlling the time at which the device is inserted into the sample chamber, there is greater control over mixing of the sample with the reagents, and the length and efficiency of extraction. (Declaration of Richard H. Schwartz at ¶ 4). This results in greater sensitivity of the assay, compared to assays in which sample mixing, and the length and efficiency of extraction cannot be controlled. (Declaration of Richard H. Schwartz at ¶ 4).

In contrast to the OSOM™ Strep A test strip, the QuickVue™ device contains a bulky housing for the immunodiagnostic test strip. (Declaration of Richard H. Schwartz at ¶ 4). This housing contains a sample extraction chamber in flow communication with the test strip. (Declaration of Richard H. Schwartz at ¶ 4). In this device, flow from the sample extraction chamber onto the test strip begins almost as soon as the extraction reagents are added to the sample in the sample chamber. (Declaration of Richard H.

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Schwartz at ¶ 4). In strep A tests using these devices, samples cannot be mixed as vigorously with reagents as in a separate sample chamber, and there is less time for extraction prior to initiation of the assay. (Declaration of Richard H. Schwartz at ¶ 4). This results in a lower sensitivity of the immunodiagnostic test. (Declaration of Richard H. Schwartz at ¶¶ 3, 4).

Moreover, other immunoassays in use prior to these one-step assays required further manipulation of the sample, such as pipetting or pouring, following extraction of the sample. (Declaration of Richard H. Schwartz at ¶ 6). This introduced additional sources of error into the test and required performance of the test by more qualified personnel. (Declaration of Richard H. Schwartz at ¶ 6).

In addition, because the prior art describes one-step methods using devices with unwieldy plastic housings unlikely to fit within a sample chamber small enough to obtain efficient extraction, it is not obvious to insert the immunoassay device into the sample chamber to initiate the assay.

Moreover, taken together, Imrich, Bogart, and Murray (US 3,957,436) do not teach a method for determining the presence or absence of a Streptococcus antigen, where separate immunoassay devices and an extraction chamber are provided, where the extraction solution comprises 0.2-5M sodium nitrite and 0.02-2M acetic acid, or where the solution contains a color indicator to indicate proper preparation. As discussed above, Imrich fails to teach or suggest a method for the detection of an analyte where the immunoassay test strip is not in flow communication with the extraction chamber. In addition, as noted at page 10 of the Office action mailed 9/2/98, Imrich does not teach vigorous mixing of the swab and extraction reagents for at least

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10 seconds, or an extraction solution where the addition of 0.3 M acetic acid to a color-indicator spiked 2 M sodium nitrite solution changes the color of the final extraction solution.

Applicants therefore respectfully assert that the claimed invention is not obvious in light of Imrich et al., either alone or in combination with Bogart and/or Murray.

CONCLUSION

For the reasons set forth above, Applicants believe that claims 10-20 clearly state that the claimed invention is directed to a method for detecting a Streptococcus antigen where an immunoassay device, and a separate assay chamber are provided. The claims also clearly state that the immunoassay device is inserted into the assay chamber after completion of extraction of the sample. Moreover, Applicants respectfully assert that the claims are not anticipated nor made obvious by Imrich et al., which describes only methods using devices in which the immunoassay test strip is in flow communication with the extraction chamber. Applicants thus believe that the claims are in condition for allowance.

Respectfully submitted,

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